STATE MEDICAID DUR COMMITTEE

NEWSLETTER

ANTIPLATELET AGENTS

MEDICAID DRUG USE REVIEW CRITERIA FOR OUTPATIENT USE

University of Utah College of Pharmacy

Volume 8 **Number 3**

APRIL 2000 : **Editors: Rae Dell Ashley, R.Ph., Duane Parke, R.Ph.**

Antiplatelet agents are used in ischemic cerebrovascular disease. Antiplatelet therapy reduces vascular morbidity and mortality 27% among patients with cardiovascular disease who are at high risk for recurrent illness.[1] Medications used for secondary prevention of stroke include: aspirin, dipyridamole, ticlopidine, clopidogrel and the dipyridamole/aspirin combination.

Aspirin is currently the standard of care for stroke prevention in patients with identified atherothrombotic disease.[2] Ticlopidine is available as alternative therapy, but serious side effects such as neutropenia limit its usefulness. Clopidogrel, a new thienopyridine derivative similar to ticlopidine, reduces the risk of stroke 7.3% over aspirin (p=NS).[3] Because of high drug cost, clopidogrel should be reserved for patients who fail aspirin or cannot tolerate it. Long term safety data for clopidogrel are limited to 3 years where as aspirin has been used for more than 100 years.[4] The combination of dipyridamole and aspirin reduced the risk of stroke by 37% compared with aspirin alone (22%) and dipyridamole alone (24%).[5] No head to head trials compare ticlopidine, clopidogrel, dipyridamole/aspirin, or warfarin in patients who fail aspirin monotherapy.

Aspirin reduces the risk of stroke about 25%.[1] Although aspirin has only a modest effect, it is widely applicable and accessible, inexpensive, and relatively safe. The optimal dose of aspirin is controversial. The executive summary from the FDA recommends low-dose aspirin (50 to 325 mg daily) for the prevention of stroke.[6] These recommendations are based on results from the Swedish Aspirin Low Dose Trial, the Second European Stroke Prevention Trial, and the United Kingdom Transient Ischemic Attack Aspirin Trial.[7,8,9]

Common side effects of aspirin include gastrointestinal irritation or ulceration, anaphylaxis, bronchospasm, and decreased renal function. The gastrointestinal toxicity of aspirin is dose related but even low dose aspirin slightly increases the risk of major bleeding.[10] For those unable to tolerate aspirin 325 mg/day because of minor dyspepsia, the options include taking aspirin with meals, using an enteric-coated formulation or taking a lower dose. For patients who experience an initial or recurrent TIA while taking aspirin, there is no evidence that increasing the dose of aspirin or changing to another antiplatelet agent will reduce the risk of subsequent stroke.[2]

The thienopyridines, ticlopidine and clopidogrel, inhibit platelet aggregation. Clopidogrel is 50 to 100 times as potent as ticlopidine in inhibiting thrombosis and prolonging bleeding time. It takes 7 to 10 days for platelet function to return to normal after exposure to aspirin, ticlopidine, and clopidogrel; this time course corresponds to the life span of the circulating platelet.[11]

Clopidogrel 75 mg per day was compared to aspirin 325 mg per day in 19,185 patients with recent ischemic stroke or myocardial infarction or patients who had symptomatic atherosclerotic peripheral arterial disease.[3] The primary outcome was first occurrence of ischemic stroke, myocardial infarction, or death. Clopidogrel reduced the risk of the primary outcome occurring by 8.7% (p=0.043). For patients in the stroke subgroup, the relative risk reduction was 7.3% (p=0.26). Compared with aspirin, clopidogrel had a smaller relative risk reduction for stroke than ticlopidine (7.3% vs. 21%).[3,12] The side effect profile of clopidogrel is similar to aspirin.

Ticlopidine 250 mg bid was compared to aspirin 650 mg bid in 3069 patients with a recent TIA or minor stroke.[12] According to an intention to treat analysis, the overall risk reduction of fatal and nonfatal stroke by ticlopidine at 3 years was 21%. A subgroup analysis of this study showed that ticlopidine was particularly effective in patients who had been taking aspirin or anticoagulant therapy at the time of cerebral ischemic event. Other studies comparing aspirin to ticlopidine favored ticlopidine by 10%; however the results were not statistically significant.

Adverse reactions of ticlopidine include changes in liver enzymes, diarrhea, dyspepsia, abdominal cramps, nausea, and anorexia.[13] Reducing the dose may lessen the diarrhea and taking the medication with meals reduces other gastrointestinal symptoms.

Severe neutropenia, thrombocytopenia, aplastic anemia, and thrombotic thrombocytopenic purpura have been reported with ticlopidine. The incidence of severe neutropenia with clopidogrel is similar to that with aspirin (0.04% vs. 0.02%) and less than that reported with ticlopidine (0.8%).[3,11] The neutropenia appears 27 to 60 days after starting therapy and is probably secondary to an arrested maturation of bone marrow myeloid precursors due to either a toxic or hypersensitivity reaction. The neutrophil count normalizes 4 to 21 days after stopping the drug.[12] Due to the adverse effect profile, ticlopidine should not be used as a first-line agent for stroke prevention.

Dipyridamole is a vasodilator which also exhibits antiplatelet effects. Dipyridamole inhibits platelet aggregation by interfering with the products of arachidonic acid metabolism, specifically thromboxane A_2 and prostacyclin PGI_2. Dipyridamole inhibits phosphodiesterase to increase levels of cyclic AMP in the platelet. This potentiates the platelet de-aggregating effect of prostacyclin. Dipyridamole also inhibits erythrocyte uptake of adenosine and adenosine metabolism. Common adverse effects of dipyridamole include: diarrhea, dizziness, lightheadedness and headache, exacerbation of angina pectoris, and blood pressure lability.[14] Dipyridamole alone is not effective for preventing stroke or other types of thrombosis.[15] It has generally been studied in combination with other agents like aspirin or warfarin. Dipyridamole alone should not be used as a first-line agent for stroke prevention.

The combination product Aggrenox® (dipyridamole extended-release 75 mg and aspirin 25 mg) was recently marketed. Fourteen trials have compared the combination of dipyridamole and aspirin versus aspirin alone.[1,22] The doses commonly used were aspirin 900 to 1300 mg per day and dipyridamole 150 to 300 mg/day. No significant differences were found between the groups. For vascular events (nonfatal stroke, nonfatal MI, or vascular death), there was a trend favoring aspirin alone and for nonfatal stroke there was a trend favoring the combination.

The most recent trial (ESPS-2) was a two-year, randomized, double-blind trial in 6602 patients who had a TIA or completed ischemic stroke.[15] Aspirin 25 mg bid, extended release dipyridamole alone 200 mg bid, or the combination of the two agents were compared. This is the only trial evaluating the marketed dose of Aggrenox®. Endpoints for the study were: stroke, death, and stroke or death. Dipyridamole plus aspirin reduced the risk of stroke by 23% over aspirin alone. Although the results are promising, controversy has surrounded this study. The original publication was rejected by Lancet due to ethical concerns and one investigator was charged with falsifying and creating data.[16] Four hundred thirty eight patients from one center were excluded from data analysis.

The most common adverse reactions reported with Aggenox® include headache, diarrhea, and dizziness. The incidence of bleeding at any site was 8.7% with the combination versus 8.2% with aspirin monotherapy.[9] In the ESPS-2 trial, one in four patients randomized to either dipyridamole or Aggrenox® withdrew from the study.

Because earlier trials comparing aspirin alone to aspirin plus dipyridamole showed no difference between the groups and the limitations of the ESPS-2 study, the combination cannot currently be recommended as first line therapy for stroke prevention.

In conclusion, aspirin is the drug of choice for stroke prevention. For patients who do not tolerate aspirin, clopidogrel would be an alternative. For patients who experience a recurrent TIA while taking aspirin, there is no evidence that changing to another antiplatelet agent will reduce the risk of subsequent stroke. The role of Aggrenox® in stroke prevention is not well defined. Some practitioners may prefer to switch patients to Aggrenox® if the patient has had a subsequent stroke on aspirin, but there is no evidence to support this action.

1 **Indication for use**

Antiplatelet agents are used for a variety of cerebrovascular and cardiovascular disorders including prevention of myocardial infarction and use in cardiovascular stenting. This review will address the use of these agents in managing stroke.

1. Duration of therapy

Most patients will require indefinite treatment.

2. Duplicative therapy

Duplicative therapy is not indicated unless the patient has a subsequent stroke on the preventative antiplatelet agent. If the patient does develop a stroke, then most clinicians empirically either increase the aspirin dose or add a secondary agent (e.g., dipyridamole) or change to another agent (e.g., clopidogrel); however, this is not evidence based.

Table 1. Antiplatelet agents- usual and maximum dosage [13,14,17,18]

Drug	Dosage Form(s)	Usual Dose for Stroke Prevention	Maximum Daily Dose for Stroke Prevention	Cost
Aspirin	Enteric coated tablets: 81 mg, 165 mg, 325 mg, 500 mg, 650 mg, 975 mg. Chewable tablets: 81 mg. Tablets: 325 mg, 500 mg. Extended release 650 mg. Controlled release 800 mg. Delayed release tablet: 81 mg. Suppositories 120 mg, 200 mg, 300 mg, and 600 mg. Buffered aspirin 325 mg, 500 mg.	81 mg/d to 325 mg/d	1300 mg per day- higher doses of aspirin are not superior to lower doses. For patients who experience an initial or recurrent TIA while taking aspirin, there is no evidence to support increasing the dose.	
Clopidogrel (Plavix®)	Tablets: 75 mg	75 mg once daily	75 mg once daily- higher doses do not result in further platelet impairment.	
Dipyridamole (Persantine®)	Tablets: 25 mg, 50 mg, 75 mg	150 - 400 mg/day	400 mg per day	
Dipyridamole Extended Release/Aspirin (Aggrenox®)	Capsule: 200 mg dipyridamole/25 mg aspirin	1 cap bid	1 cap bid	
Ticlopidine (Ticlid®)	Tablets: 250 mg	250 mg bid	250 mg bid; higher doses do not result in further platelet impairment.	

3. Drug-drug interactions

The following list describes clinically significant drug-drug interactions with the antiplatelet agents.[24-28]

d. **Antacids-** Antacids increase urinary pH and reduce the renal reabsorption of **aspirin** thus increasing clearance and decreasing the pharmacological effects. The magnitude of the antacid interaction depends on the agent, dose and pretreatment urinary pH. Giving **ticlopidine** after antacids has resulted in an 18% decrease in ticlopidine plasma levels. Ticlopidine should be taken 1-2 hours before antacid dose. **Antacids, H2-receptor blockers, proton pump inhibitors** raise the gastric pH significantly and reduce the bioavailability of **dipyridamole**.

e. **Urinary alkalinizers** (e.g., sodium bicarbonate) may decrease the pharmacological effects of salicylates. The magnitude of the antacid interaction depends on the agent, dose and pretreatment urinary pH. Antacids and urinary alkalinizers increase urinary pH and reduce the renal reabsorption of salicylate thus increasing salicylate clearance.

f. **Carbonic anhydrase inhibitors-** When oral **acetazolomide or diclofenamide** were given in combination with high dose **aspirin** (3.9 gm) salicylate intoxication occurred. Also, carbonic anhydrase inhibitors accumulate and may result in CNS depression and metabolic acidosis.

g. **Corticosteroids- Betamethasone, dexamethasone, prednisone, prednisolone, methylprednisolone and hydrocortisone** may increase risk of GI ulceration and increase salicylate clearance and decrease serum effectiveness; tailor salicylate dosage as needed. Monitor for salicylate toxicity if taking large doses of aspirin and tapering corticosteroid dosage down.

h. **Oral Anticoagulants- Warfarin** and **aspirin** may have additive hypoprothrombinemic effect and since aspirin impairs platelet function there is potential increased risk of bleeding. **Ticlopidine** inhibits R-warfarin metabolism and platelet aggregation with potential increased risk of bleeding; monitor INR regularly. **Clopidogrel** prolongs bleeding time and at high concentrations, clopidogrel may inhibit CYP2C9 and decrease the metabolism of warfarin. Concomitant administration of **dipyridamole** and **warfarin** does not appear to increase the frequency or severity of bleeding compared to warfarin alone.

i. **Heparin- Aspirin** can increase risk of bleeding in heparin anticoagulated patients. The safety of heparin and **clopidogrel** has not been established, monitor patients closely. **Danaparoid and low molecular weight heparin** like **enoxaparin** given with **dipyridamole** may result in increased risk of bleeding and increase risk of hematoma when neuroaxial anesthesia is employed.

j. **NSAIDs-** The combination of **NSAIDs with aspirin, clopidogrel, ticlopidine and dypyridamole/aspirin** may result in increased incidence of bleeding. The combination of **indomethacin and dipyridamole** may result in significantly reduced urine volume, sodium excretion, and renal filtration fraction leading to marked fluid retention. Monitor renal function especially in patients with cardiac or vascular problems.

k. **Aspirin-** The combination of **ticlopidine** and **aspirin** or **clopidogrel** and **aspirin** may result in increased bleeding; monitor patients for signs and symptoms of bleeding.

l. **Antihypertensive agents**- Effectiveness of **beta-blockers (e.g., propranolol, pindolol, labetalol), and ACE inhibitors (mainly enalapril),** may be reduced when given in combination with aspirin; monitor blood pressure. **Verapamil** 240 mg daily and **aspirin** 325 mg daily has resulted in abnormal bruising and prolonged bleeding times. This combination does not need to be normally avoided unless the patient becomes symptomatic.

m. **Methotrexate-** the combination of aspirin (975 mg) and methotrexate (10 mg) may result in increased methotrexate drug levels causing toxicity by interfering with protein binding and renal elimination of the antimetabolite

n. **Probenecid and sulfinpyrazone-** Salicylates in doses greater than 700 mg antagonize the uricosuric effect of probenecid and sulfinpyrazone.

o. **Sulfonylureas and Insulin-** Salicylates in doses > 2 gm/d have a hypoglycemic action. They may potentiate the glucose lowering effect of sulfonylureas and insulin.

p. **Cyclosporine-** The combination of cyclosporine and ticlopidine may result in a reduction of cyclosporine level second to increased metabolism; monitor levels.

q. **Eptifibatide, Reteplase, Streptokinase**- Administration of ticlopidine, clopidogrel, dipyridamole with either eptifibatide, reteplase, or streptokinase may result in increased risk of bleeding.

r. **Antiepileptics-** The administration of **ticlopidine** and **phenytoin or fosphenytoin** may result in elevated phenytoin levels and possible toxicity; monitor serum levels and adjust dose. **Ticlopidine** may inhibit **carbamazepine** metabolism; monitor carbamazepine plasma levels. **Aspirin** displaces **valproic acid** from its protein binding sites and may decrease its total body clearance; monitor for symptoms of valproic acid toxicity and/or serum levels.

s. **Theophylline**- The combination of **ticlopidine** and **theophylline** may result in elevated serum theophylline levels; monitor levels. The administration of **caffeine** or **theophylline** with **dipyridamole** may negate the coronary vasodilation caused by dipyridamole and interfere with dipyridamole thallium scintigraphy tests.

t. **Agents metabolized by P450 2C9**- At high concentrations in vitro, clopidogrel inhibits p450 2C9. **Clopidogrel** may interfere with the metabolism of **phenytoin, tamoxifen, tolbutamide, torsemide**, and **fluvastatin** but there are no data to predict the magnitude of the interactions.

u. **Edrophonium, Distigmine bromide- Dipyridamole** may decrease the effectiveness of **edrophonium or distigmine bromide** and aggravate muscle weakness

v. **Adenosine**- The combination of **adenosine and dipyridamole** may result in adenosine toxicity secondary to decreased metabolism; a smaller dose of adenosine may be required.

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